Treatment Threshold for Neonatal Hypoglycemia

TO THE EDITOR: Van Kempen et al. (Feb. 6 issue)[1] report that in otherwise healthy newborns with asymptomatic moderate hypoglycemia, a lower glucose threshold (36 mg per deciliter) for treatment of the hypoglycemia was noninferior to a traditional threshold (47 mg per deciliter) with regard to psychomotor development at 18 months of age. Because the trial excluded all neonates with severe hypoglycemia before study entry, the conclusions cannot be extrapolated to all at-risk neonates who are screened for hypoglycemia. The Pediatric Endocrine Society recommendations[2] suggest a treatment target of at least 50 mg per deciliter in the first 48 hours of life for at-risk newborns with hypoglycemia. We have particular concern that the conclusions of van Kempen et al. may be mistakenly interpreted to indicate that a glucose concentration as low as 36 mg per deciliter is an adequate treatment threshold for hypoglycemia in neonates who could have a persistent hypoglycemia-related disorder, such as congenital hyperinsulinism. Thus, we strongly caution against using the results of the HypoEXIT (Hypoglycemia–Expectant Monitoring versus Intensive Treatment) trial to change guidelines or guidance for treating neonates with hypoglycemia in whom a persistent hypoglycemia disorder has not yet been ruled out.

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1. van Kempen AAMW, Eskes PF, Nuytemans DHGM, et al. Lower versus traditional treatment threshold for neonatal hypoglycemia. N Engl J Med 2020;382:534-44.
2. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. J Pediatr 2015;167:238-45.

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TO THE EDITOR: The clinical relevance of the HypoEXIT trial is limited, since long-lasting adverse effects of mild or moderate hypoglycemia on a child's neurodevelopment may become apparent only when the child reaches school age.[1] In addition, the study has an important methodologic limitation — the caregivers were aware of the group assignments. Therefore, the trial should be considered to have possible performance bias. Practitioners' convictions about the glycemic target may have unconsciously influenced their conduct, the more so since the study protocol left the precise intervention to the discretion of each attending physician. Masking of group assignments could have been ensured effectively if the laboratory glucose measurements had been reported to each clinician as being 5 mg per deciliter lower in the traditional-threshold group and 5 mg per deciliter higher in the lower-threshold group. Then, a plasma glucose treatment threshold of 41 mg per deciliter or higher would have been the same in the two treatment groups, thus preventing any unintentional preference for either strategy. The importance of masking cannot be overestimated, since a noninferiority trial is not conservative in nature.[2]

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1. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology 2019;115:116-26.
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TO THE EDITOR: Van Kempen et al. contribute important data to the controversy of treatment thresholds for neonatal hypoglycemia. However, we have concerns regarding their conclusions.

First, it is known that subtle neurodevelopmental consequences of neonatal hypoglycemia will not manifest until later in childhood — for example, as inferior executive functioning and visual–motor functioning at 4.5 years of age[1] or as poorer school performance in fourth grade.[2] Second, the authors observed a greater prevalence of frequent (≥4 episodes after randomization) hypoglycemia (four times higher prevalence) and severe hypoglycemia (two times higher prevalence) in the lower-threshold group than in the higher-threshold group, and both frequent and severe hypoglycemia have been shown in other studies to be associated with adverse neurodevelopmental outcomes later in life.[1,3]

Although the study provides reassuring data, the overall evidence for the safety of current management strategies for neonatal hypoglycemia with respect to long-term outcome remains limited. Balancing risks and benefits between overtreatment and potential neurodevelopmental impairment, we still recommend using the traditional threshold (47 mg per deciliter), as recommended in the majority of recent guidelines,[4] following the maxim "primum non nocere" — at least until the follow-up trial validates the favorable outcome for the lower-threshold group later in life.

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THE AUTHORS REPLY: Thornton and colleagues are concerned that the results of the HypoEXIT trial may be inappropriately extrapolated to all newborns with hypoglycemia, especially when an underlying persistent hypoglycemia disorder has not yet been ruled out. We thank our colleagues for highlighting this important caveat. It is exactly why we emphasized that a treatment threshold value of 36 mg per deciliter should not be regarded as safe under all circumstances and — in accordance with the Pediatric Endocrine Society guideline — stressed the need for a higher target glucose concentration in newborns with (suspected) endocrine or metabolic disorders.

Degraeuwe expresses concern about the possibility of performance bias undermining our study. When the caregivers are aware of the child's group assignment, performance bias can be caused by poor adherence, use of concomitant treatments, and protocol violations.[1] During the initiation visits of the HypoEXIT trial, we confirmed by discussion that all participating physicians were truly in equipoise. This makes poor adherence (e.g., letting children cross over to the other group) less likely. A between-group comparison of our prospectively defined secondary outcomes shows fewer treatment interventions in the lower-threshold group, along with lower mean glucose concentrations and more hypoglycemic episodes. These findings indicate the existence of a true contrast between the treatment groups, despite the fact that the caregivers in our study were aware of the patients' assigned groups. Although we cannot completely rule out performance bias, there is no evidence that dilution of the contrasts between the treatment groups — biasing the results toward noninferiority — occurred in this trial.

We agree with Degraeuwe and with Roeper and colleagues that long-term follow-up studies are needed, since many facets of psychomotor development emerge later in childhood. The studies mentioned by Roeper and colleagues are cohort studies in which newborns with hypoglycemia were compared with newborns with normoglycemia. In this context, cohort studies are susceptible to selection bias, information bias,

and confounding. Specifically, differences between the study groups in baseline characteristics, absence of a clear treatment protocol, and presence of (residual) confounding may impair correct inferences.[2,3] This is why, for many years, experts in this field have called for carefully designed randomized, controlled trials.[2-5] The rationale of our study was based on the need to, as Roeper et al. state, balance the risks and benefits of undertreatment and overtreatment in preventing neurodevelopmental injury by using a minimally biased study design. We felt that in this context, "primum non nocere" goes for both undertreatment and overtreatment.

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Since publication of their article, the authors report no further potential conflict of interest.

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